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The Beckwith-Wiedemann Syndrome Phenotype and the Risk of Cancer

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Beckwith-Wiedemann syndrome (BWS) comprises of a number of childhood abnormalities, often associated with one or more tumors. Thirty-eight patients were investigated to determine clinical and/or biological signs associated with a tumor presence. Our patients exhibited a higher incidence of tumor development (21%) than that previously reported, underlying the care with which such patients should be followed, when particular clinical features are observed: visceromegaly affecting three organs (liver, kidney, spleen), and also family history (with sign of BWS such as macroglossia, omphalocele, hemihypertrophy, embryonic tumor), high body weight at birth (≥ +2 standard deviations) and diastasis recti. Med. Pediatr. Oncol. 28:411–415, 1997.

Key words: Beckwith-Wiedemann syndrome; insulin-like growth factor; tumor

INTRODUCTION

A childhood syndrome with characteristic abnormalities was first reported by Beckwith [1] and Wiedemann [2] and has since been described elsewhere [3,4,5]. The incidence of the Beckwith-Wiedemann syndrome (BWS) has been estimated to be 1:13,700 births [6]. The BWS appears to include a wide spectrum of anomalies (neonatal gigantism, omphalocele, macroglossia, visceromegaly, hemihypertrophy, and neonatal hypoglycemia . . .) and not all of them are present in all cases. The patients are also predisposed to (mostly intra-abdominal) malignancies, with a risk estimate of about 7.5% [7].

Family studies indicate linkage of the BWS locus to the marker 11p15.5 [8,9] and the IGF-II gene located at this locus has been suggested as a candidate for the BWS gene [10]. Increased levels of IGF-II mRNA have been detected in numerous human tumors often associated with the BWS, such as nephroblastomas, neuroblastomas, rhabdomyosarcomas, and adrenocortical carcinomas [11–14]. Both the murine and the human IGF-II genes are subject to differential genomic imprinting, and only the paternal allele is expressed [15–17]. In some patients with BWS, paternal isodisomy on the short arm of chromosome 11 has been described and can be used as a predictive molecular sign for tumor appearance [18, 19].

As tumor frequency is high among BWS patients, we investigated whether or not some clinical and biological (serum IGF levels) features can be used to predict risk of tumor appearance.

PATIENTS

Thirty-eight patients (18 boys and 20 girls) diagnosed as having BWS and admitted to various departments of the Trousseau children's hospital were included in the study. The BWS symptoms which led to presentation at the hospital and department to which patients were referred are given in Figure 1. The 11p15 locus in genomic DNA had previously been analyzed for 23 of the patients [18].

METHODS

IGF Assays

Serum IGF levels were determined after separation by acidic gel filtration using methods described previously [20]. IGF-I was measured by radioimmunoassay (anti-IGF-I antibodies were kindly provided by Dr. F. Frankenne and Dr. G. Hennen, Centre Hospitalier de Liège, Belgium) and IGF-II by protein-binding assay using a cerebrospinal fluid binding protein with a selective affinity for IGF-II [21]. IGF-I and IGF-II used both as standard and as tracer were generously provided by CIBA-GEIGY Ltd. (Basel, Switzerland).

Statistical Analysis

Odds ratios were used for statistical analysis and confidences intervals calculated.

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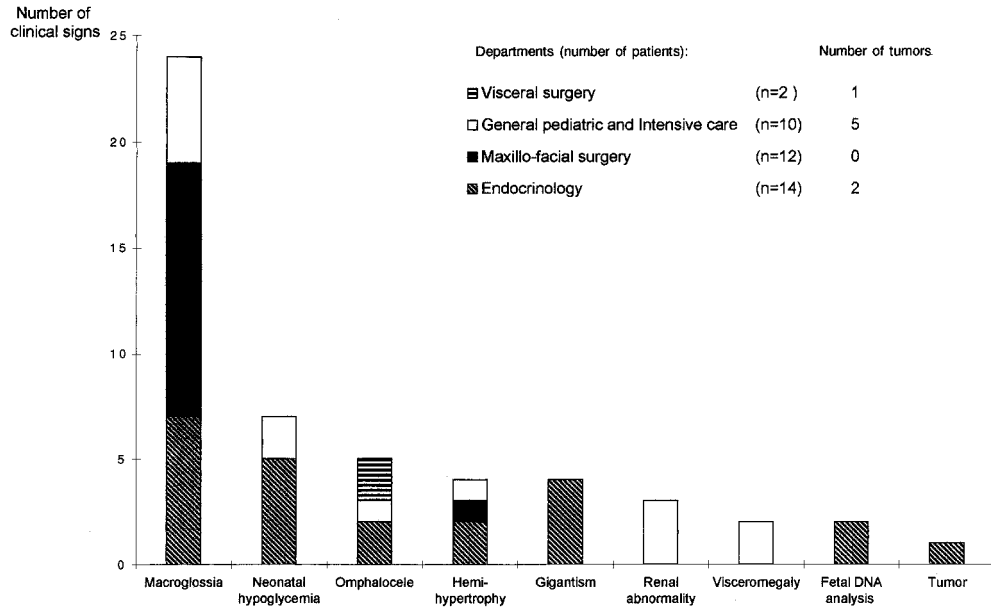

Fig. 1. Problems first leading to medical observation in the different departments of the hospital.

RESULTS

Eight of the 38 patients (21%) had tumors, nephroblastomas being the most frequently observed (5/8). Five tumors were detected in patients under 2-years-old and 3 in children about 4 to 5-years-old (Table I). Moreover, the delay between the appearance of the first clinical sign leading to the diagnosis of BWS and a tumor detection was in all cases less than 5 years (Table I).

Among the various clinical signs observed, those more frequently found among BWS patients with a tumor were: macroglossia, elevated birth weight, polyvisceromegaly (mainly liver, kidney, and spleen), abdominal wall defects, facial abnormality and family history (Table II). However, only visceromegaly affecting 3 organs was significantly associated with the presence of tumor (Table II). The number of tumor 8 being low, the odd ratio test led to very large confidence intervals. Thus it is interesting to note that family history, high birth weight ($\geqslant +2$ SD), and diastasis recti were very close to a significant association with tumor presence.

Among the 26 families for whom a family history was available, one of the signs associated with BWS (macroglossia, hemihypertrophy, omphalocele, and embryonic tumor generally neuroblastoma) was detected in at least a second member of 13 families (50%). The affected family member(s) was a parent or sibling of the BWS child: 5 cases from paternal side, 3 cases from maternal side, 1 from both sides and in 4 cases a brother or sister. Moreover, a family history was more frequent among cases with or without tumor (6/7 ie 85.7%).

Macroglossia, the major symptom of BWS [22], was present in 92.1% of our patients (35/38) (Table II). The enlarged tongue in some cases needed to be reduced because of effects on nutrition and for esthetic reasons. Partial glossectomy was required for 37% of the 38 patients and in 50% of the patients with tumor.

The post-natal gigantism (height more than 2 standard deviations above normal) was observed for 17 children from 7 months to 12-years-old (mean = 4.2 years ± 3.3 SD). Neonatal hypoglycemia was symptomatic for 5 children and detected biologically for 10 cases (blood glucose below 2.7 mmol/l) and rapidly decreased with time for most of the cases.

Serum IGF-I and IGF-II levels were measured in 27 patients (Fig. 2A and 2B). IGF-I and IGF-II levels were within the normal range for the age for most of the patients. However, one patient without tumor had an IGF-I level in the lower part of the normal range and another patient who had a tumor had a very low level for her age (Fig. 2A). For 3 other patients, IGF-II levels were high (Fig. 2B). Among these 3 patients with abnormal IGF-II level and normal IGF-I value, only one had tumor.

DISCUSSION

Clinical and biological data from 38 patients diagnosed as suffering from BWS were analyzed to evaluate whether various signs are predictors of tumors associated with this syndrome.

The incidence of anomalies among our cases was very similar than previously reported in the literature [3,4] indicating that the same type of BWS populations were investigated by these studies. Not every anomaly appears in all cases and some are more frequent than others. The most common characteristics in our patients were mac-

TABLE I. Tumor Type and Age of BWS Patients When a Tumor Was Detected and the Delay Between First BWS Sign and Tumor Detection

	Tumor	Age of the patient at tumor detection	Delay between first sign of BWS and tumor detection
Patients with Beckwith-Wiedemann syndrome	1 - Neuroblastoma Nephroblastoma	1st: 1 month 2nd: 1 year	1 month
	2 - Nephroblastoma (bilateral)	11 months	11 months
	3 - Nephroblastoma	1 year	6 months
	4 - Nephroblastoma	4 years	4 years
	5 - Nephroblastoma	5 years	5 years
	6 - Neuroblastoma	10 months	10 months
	7 - Ganglioneuroma	4 years	3 9/12 years
	8 - Adrenocortical carcinoma	1st: 1 5/12 year (left side) 2nd: 5 8/12 years (right side)	0 4 3/12 years

TABLE II. Comparison of the Major Clinical Signs in Beckwith-Wiedemann Syndrome Patients Without or With Tumors

	BWS Patients without tumor (n = 30)	BWS Patients with tumor (n = 8)	Odd Ratio (OR)	Ln OR	Confidence Intervals
Sex M	14	4	1.11	0.11	−1.42; 8.42
Sex F	16	4	0.90	−0.11	−1.63; 8.66
Family history	7/19	6/7	6.00	1.79[b]	−0.46; 8.86[b]
Macroglossia	27	8	—	—	—
Birth weight ⩾+2 SD	9/22	7	5.69	1.74[b]	−0.48; 9.58[b]
Post-natal gigantism ⩾+2 SD	14/28	3	0.67	−0.40	1.97; 7.68
Neonatal hypoglycemia	12/28	3	0.84	−0.17	−1.75; 7.42
Visceromegaly	14	5	1.67	0.51	−1.06; 9.05
—affecting 1 organ	7	0	—	—	—
—affecting 2 organs	5	1	0.76	−0.27	−2.54; 4.53
—affecting 3 organs	2	4	5.33	1.67[a]	0.04; 6.47[a]
Abdominal wall defect	20	6	1.38	0.33	−1.41; 10.32
—omphalocele	6	1	0.63	−0.46	−2.71; 4.73
—umbilical hernia	9	3	1.30	0.26	−1.32; 7.05
—diastasis recti	9	5	2.86	1.05[b]	−0.53; 8.38[b]
Hemihypertrophy	5	2	1.48	0.39	−1.41; 5.58
Facial abnormality:	15	5	1.50	0.41	−1.16; 9.17
—ear	12	5	2.06	0.72	−0.85; 8.80
—nevus flammeus	10	0	—	—	—
—mid-face hypoplasia	13	4	1.24	0.21	−1.32; 8.29
Genital abnormality:					
—cryptorchidism	10/14	2/4	0.50	−0.69	−2.88; 6.10
—clitoromegaly	0/15	1/4	6.00	1.79	−1.24; 3.75
Renal-urinary abnormality:	5	3	2.25	0.81	−0.82; 6.35
Hydramnios	6	2	1.25	0.22	−1.58; 5.77

[a]Significant confidence interval of the LnOR.
[b]LnOR and confidence intervals close to a significance.

roglossia (92.1%), abdominal wall defects (68.4%), high birth weight (53.3%), facial abnormality (52.6%), family history (50%), and visceromegaly (50%).

Tumors were found in 8 of our 38 patients (21%) which is a higher incidence than in previous series: 5% (1/20) by Pettenati et al. (4), 7.5% (29/388) by Wiedemann HR (7), and 10% (20/200, reported cases) by Sotelo-Avila et al [3]. Unlike previous series, we report the recruiting department for each patient. Our results do not seem to reflect a particular selection bias of patients as a much smaller proportion was initially admitted to the Visceral Surgery Department (n = 2, omphaloceles) than to other departments: General Pediatric and Intensive Care (n = 10), Maxillo-facial Surgery (n = 12) or Endocrinology (n = 14) (Fig. 1). However, our pediatric hospital is a referral center and thus possibly receives the more severely affected cases which could explain the higher incidence of tumors. Even if this population has been selected, it is nevertheless valuable to report the most frequent clinical signs observed among patients with BWS and an associated tumor.

Wiedemann previously reported the prognostic impor-

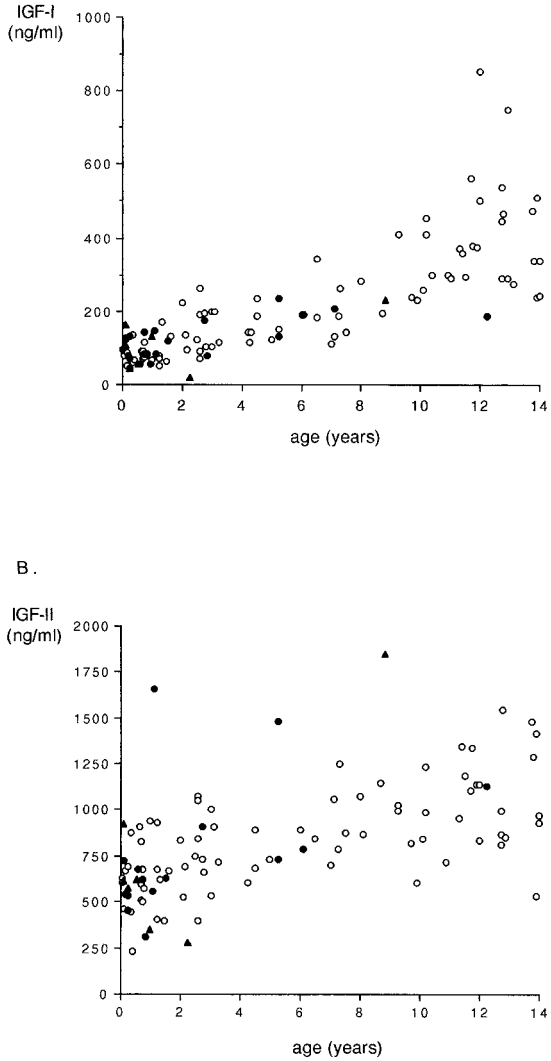

Fig. 2. A. Serum IGF-I levels in BWS patients without (●) or with tumor (▲) (n = 27). IGF-I levels for control children (○) are shown (n = 94). B. Serum IGF-II levels in BWS patients without (●) or with tumor (▲) (n = 22). IGF-II levels for control children (○) are shown (n = 87).

tance of hemihypertrophy which is present in more than 40% of the BWS children with neoplasm and only in 12.5% of all children with BWS [7]. In our study, other clinical signs were present with a higher frequency in BWS patients with tumors (n = 8) than BWS patients without tumor (n = 30) (Table II). In particular, visceromegaly affecting 3 organs (liver, kidney, and spleen), was significantly associated with the presence of tumor (Table II). This sign could be a useful predictive indicator for a risk of tumor. The relationship between family history, elevated birth weight, diastasis recti, and the appearance of a tumor were non statistically significative; however, BWS is a very rare syndrome and we enrolled only few cases such that associations close to significance should be taken into account.

Information concerning family history was available for 26 of the 38 families. Thirteen had other members presenting signs associated with BWS. The additional affected members in these 13 families (macroglossia, hemihypertrophy, omphalocele, and embryonic tumor: neuroblastoma) were found 5 times from paternal side, 3 times from maternal side, 1 from both sides and in 4 cases this was found in the brother/or sister. This indicates that there is no maternal or paternal linkage.

An interesting finding is that family history seems to predispose to tumors: 6 tumors were observed in the 13 familial cases (Table II). However, the BWS mechanism is believed to be post-zygotic [18,19]. The rare BWS family data reported elsewhere do not indicate an association with tumor unless cytogenetic abnormality was also present [23]. Among the 13 familial cases detected, only 5 cytogenetic analysis were available and were all normal, even for the 2 cases where uniparental disomy (UPD) was detected [18]. This suggests that unlike in UPD cases where several genes might be involved, abnormalities such as a single gene mutation or small deletion could be genetically transmitted and predispose to post-zygotic abnormalities: UPD and/or tumors.

It was previously shown that genomic analysis at the 11p15 locus, where the IGF-II gene maps, is also useful for predicting tumor risk. Analysis for genomic DNA prepared from blood or tissue samples (such as tongue after partial glossectomy) revealed anomalies including UPD in 20% of all BWS patients [18,19]. Seventy-five percent of these cases with UPD also suffered from a tumor [18]. However, several BWS patients with tumor but without UPD were described. Therefore, there may be other useful prognostic factors for tumor risk other than UPD.

Serum IGF-I and IGF-II levels were in the normal range for most of our patients indicating no correlation with tumor appearance. Thus, IGF levels including IGF-II are of no value for tumor prediction.

The clinical signs described here (visceromegaly of at least 3 organs, family history, elevated birth weight, and also to a lesser degree, abdominal wall defects) help to predict tumor development: the presence of one of these signs in a BWS patient suggests tumoral potentiality. Because of the high risk of tumor in the BWS, every patient needs to be thoroughly investigated by physical examination and ultrasonography, at least until six-years-old, and if some of the clinical signs mentioned above are detected (visceromegaly of more than three organs, elevated body weight at birth, family history, or molecular signs (paternal isodisomy)) the examination should be frequent.

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